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Mechanisms of Acute Lumen Gain and Recurrent Restenosis After Rotational Atherectomy of Diffuse In-Stent Restenosis

A Quantitative Angiographic and Intravascular Ultrasound Study

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OBJECTIVES This quantitative angiographic and intravascular ultrasound study determined the mechanisms of acute lumen enlargement and recurrent restenosis after rotational atherectomy (RA) with adjunct percutaneous transluminal coronary angioplasty in the treatment of diffuse in-stent restenosis (ISR).

BACKGROUND In-stent restenosis remains a significant clinical problem for which optimal treatment is under debate. Rotational atherectomy has become an alternative therapeutic approach for the treatment of diffuse ISR based on the concept of "tissue-debulking."

METHODS Rotational atherectomy with adjunct angioplasty of ISR was used in 45 patients with diffuse lesions. Quantitative coronary angiographic (QCA) analysis and sequential intravascular ultrasound (IVUS) measurements were performed in all patients. Forty patients (89%) underwent angiographic six-month follow-up.

RESULTS Rotational atherectomy lead to a decrease in maximal area of stenosis from 80 ± 32% before intervention to 54 ± 21% after RA ($p < 0.0001$) as a result of a significant decrease in intimal hyperplasia cross-sectional area (CSA). The minimal lumen diameter after RA remained 15 ± 4% smaller than the burr diameter used, indicating acute neointimal recoil. Additional angioplasty led to a further decrease in area of stenosis to 38 ± 12% due to a significant increase in stent CSA. At six-month angiographic follow-up, recurrent restenosis rate was 45%. Lesion and stent length, preinterventional diameter stenosis and amount of acute neointimal recoil were associated with a higher rate of recurrent restenosis.

CONCLUSIONS Rotational atherectomy of ISR leads to acute lumen gain by effective plaque removal. Adjunct angioplasty results in additional lumen gain by further stent expansion and tissue extrusion. Stent and lesion length, severity of ISR and acute neointimal recoil are predictors of recurrent restenosis. (J Am Coll Cardiol 1999;34:33–9) © 1999 by the American College of Cardiology

Coronary stent implantation has markedly improved acute and long-term outcome after coronary angioplasty (1,2). Widening of the indication for stent implantation (3) led to a significant increase in implantation numbers and disclosed in-stent restenosis (ISR) as a new, iatrogenic entity, which developed into a considerable problem in interventional cardiology. In contrast to angioplasty, where restenosis is predominantly caused by elastic recoil and vascular remodeling, ISR is almost exclusively attributable to neointimal hyperplasia (4,5). The optimal percutaneous treatment of ISR remains unclear, especially when it presents as a severe and diffuse process. At present, additional angioplasty is the treatment of choice for focal lesions (6,7). In long and diffuse restenotic stents, however, angioplasty may result in unacceptably high restenosis rates of up to 80% (8). Therefore, debulking techniques (excimer laser angioplasty, directional coronary atherectomy, rotational atherectomy), ablating intrastent neointimal tissue before adjunct angioplasty, may have theoretical advantages.

Rotational atherectomy (RA) has primarily been designed for "differential cutting," the treatment of heavily calcified lesions in native coronary arteries (9,10). Previous intravascular ultrasound (IVUS) studies, however, have shown that RA also effectively ablates noncalcified plaque (11), implicating a potential role for this technique in the treatment of ISR.

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Abbreviations and Acronyms

CSA = cross-sectional area
EEM = external elastic membrane
IH = intimal hyperplasia
ISR = in-stent restenosis
IVUS = intravascular ultrasound
MLD = minimal lumen diameter
QCA = quantitative coronary angiography
RA = rotational atherectomy

The purpose of the present study was to use serial intravascular ultrasound analysis as well as quantitative coronary angiography (QCA) to assess the mechanisms of acute lumen gain after RA with additional angioplasty in the treatment of diffuse ISR. In addition, systematic angiographic follow-up was performed to identify clinical, procedural, angiographic and IVUS predictors of recurrent restenosis.

METHODS

Patient and lesion characteristics. A total of 45 patients (49 lesions) with a mean age of 60 ± 11 years (29 men, 16 women) were studied. Their cardiovascular risk profile was: 89% arterial hypertension, 82% hypercholesterolemia, 51% smokers and 38% diabetics. Forty patients presented with stable angina; the remaining had unstable angina. The mean total stent length was 29.5 ± 19.2 mm (range 7 to 65 mm), and consisted of 2.1 ± 1.2 (range 1 to 6) primarily implanted stents per lesion (mean balloon size for implantation: 3.0 ± 0.7 mm). There were 37 Palmaz-Schatz, 44 ACS MultiLink, 14 PURA and 8 Wallstents. The mean lesion length was 22.4 ± 20.2 mm, with 46/49 (94%) lesions >10 mm, indicating diffuse ISR. Arteries treated and imaged were left anterior descending in 19, left circumflex in 9 and right coronary artery in 17 patients. None of the lesions was in a saphenous vein graft or ostial in location.

Rotational atherectomy was performed 7.3 ± 1.0 months after primary stent implantation. Measurements of creatine kinase were performed at baseline, and 6 and 12 h postprocedure. Follow-up angiography was obtained in 40/45 patients (89%) at 5.8 ± 1.5 months after repeat intervention. Clinical follow-up for the remaining five patients was completed by telephone contact.

Patients were prospectively studied with a protocol that had been approved by the institutional ethics committee and patients gave written informed consent before participation.

Rotational atherectomy with adjunct angioplasty procedure. Details of the rotablator technique have been described elsewhere (9,10). In contrast to RA in native coronary arteries, the system (Rotablator system, Scimed, Redmond, Washington) was adjusted to a submaximal rotational speed between 150,000 and 170,000 rounds per minute, taking great care to avoid drops >5,000 rounds. Advancement distal to the stenosis into the previously untreated and unstented vessel segment was carefully avoided. Intracoronary nitroglycerin was given liberally in 0.2-mg bolus doses before and after each passage. A step approach with increasing burr sizes and 2.3 ± 1.0 burrs/lesion (range 1 to 4) with a mean burr size of 1.9 ± 0.5 mm (range 1.25 to 2.38 mm) and a final burr size of 2.05 ± 0.5 mm was performed. The final burr/artery (stent) ratio by IVUS measured 0.8 ± 0.4. Adjunct balloon angioplasty (maximum pressure: 7 ± 1 atm) was performed with a mean balloon size of 3.0 ± 0.6 mm (balloon/artery ratio: 1.3 ± 0.3).

Quantitative coronary angiography analysis: procedural success and recurrent restenosis. Quantitative coronary angiography analysis was performed off-line with an automated edge-detection algorithm (CAAS II System, Pie-Medical, Maastricht, The Netherlands) with the outer diameter of the contrast-filled catheter used as the calibration standard. The following measurements were obtained: reference diameter, minimal lumen diameter (MLD) within the lesion (mm), mean (overall) luminal diameter of the total stent length (mm) and percent diameter stenosis before intervention, after RA, after angioplasty and at follow-up in multiple projections. The results from the worst view were analyzed. The lesion length was measured as the distance from shoulder to shoulder in all available projections. The longest lesion length was recorded to avoid effects of foreshortening. Due to the complexity and length of many of the lesions with involvement of adjacent segments proximal and distal, a user-defined reference luminal diameter of a proximal and distal angiographically normal appearing segment was chosen.

Procedural success was defined as a final diameter stenosis <50% without major in-hospital complications (death, bypass surgery, additional angioplasty or Q-wave myocardial infarction). Recurrent restenosis after RA at follow-up angiography was defined as ≥50% diameter stenosis.

Intravascular ultrasound imaging protocol. Studies were performed using a single-element 30-MHz transducer within either a 2.9-F long monorail/common distal lumen imaging sheath or within a 3.2-F short monorail imaging sheath (Boston Scientific Corp.) and an automated pullback with a speed of 0.5 mm/s to obtain a complete and homogeneous image sequence.

Intravascular ultrasound imaging was started 2 min after intracoronary administration of 0.2 mg nitroglycerin. The ultrasound catheter was advanced beyond the target lesion and an imaging run was performed to the aorto-ostial junction. Image quality was adjusted to the relatively low echogenic in-stent neointima during catheter advancement to ensure optimal visualization. Studies were recorded during transducer pullback on high resolution S-VHS tape for off-line analysis.

Table 1. Quantitative Angiography Acute and Follow-up Results (40 Patients) and Planar Intravascular Ultrasound (45 Patients) Procedural Results of Rotational Atherectomy With Adjunct Percutaneous Transluminal Coronary Angioplasty (PTCA) for Diffuse In-Stent Restenosis

		Intervention		
QCA Results (mm)	**Preintervention**	**After RA**	**After PTCA**	**Follow-up**
Reference diameter	2.22 ± 0.31	2.20 ± 0.24	2.30 ± 0.32	2.20 ± 0.31
MLD	0.57 ± 0.35	1.52 ± 0.29	1.89 ± 0.21	1.05 ± 0.34
Diameter stenosis (%)	74 ± 26	31 ± 18	18 ± 14	52 ± 23
Planar IVUS results (mm^2)				**p (ANOVA)**
Reference lumen CSA	6.72 ± 0.40	6.85 ± 0.41	6.90 ± 0.44	NS
Minimal lumen CSA	1.35 ± 1.28	3.17 ± 0.70*	4.28 ± 0.61*	<0.0001
Mean lumen CSA	2.96 ± 1.10	3.67 ± 0.73†	4.81 ± 0.70*	<0.0001
Stent CSA	7.59 ± 0.78	7.60 ± 0.72	8.49 ± 0.48*	<0.0001
Intimal hyperplasia CSA	4.63 ± 0.98	3.94 ± 0.69†	3.68 ± 0.80	<0.0001
Peristent plaque CSA	8.13 ± 2.17	8.34 ± 1.99	9.67 ± 1.86†	<0.001
EEM CSA	15.71 ± 4.46	15.93 ± 4.81	18.15 ± 2.84†	<0.01
Area stenosis, max. (%)	80 ± 32	54 ± 21*	38 ± 12†	<0.0001
Area stenosis, mean (%)	56 ± 36	46 ± 29	30 ± 19†	<0.0001

*$p < 0.0001$; †$p < 0.01$, compared from preintervention to after rotational atherectomy (RA) or from after RA to after PTCA. All data are expressed as mean area ± standard deviation. ANOVA = analysis of variance; CSA = cross-sectional area; EEM = external elastic membrane; IVUS = intravascular ultrasound; max. = maximum; MLD = minimal lumen diameter; QCA = quantitative coronary angiography; RA = rotational atherectomy.

Quantitative IVUS measurements. The method of IVUS measurements has been validated in vivo and in vitro (12–14). In-stent restenosis length was defined as the axial length of the stent (in millimeters) before intervention in which intimal hyperplasia (IH) cross-sectional area (CSA) occupied >75% stent CSA. The off-line planar IVUS measurements (in mm^2) were traced in 1-mm increments and included: 1) lumen CSA; 2) stent CSA, and 3) external elastic membrane (EEM) CSA. The IH CSA was defined as the stent CSA minus lumen CSA, and peristent plaque was defined as EEM CSA minus stent CSA. The minimal and the mean lumen CSA within the stent were obtained for calculations of the pre- and postprocedural maximal and mean area stenosis. The lumen, stent, IH, peristent plaque and EEM CSA of the whole stent length were averaged per patient and compared before intervention versus after RA (maximal burr size), after RA versus after angioplasty and preintervention versus after angioplasty (postintervention). In addition, serial analysis (before intervention, after RA, after angioplasty) was performed to separate the contribution of 1) tissue ablation, 2) stent expansion and 3) tissue extrusion to the overall periprocedural lumen gain.

The MLD was defined as the smallest lumen diameter over the whole stent length and was used for calculations of acute neointimal recoil after RA. Recoil was defined as a burr size (diameter in mm)/MLD (mm) ratio >1. When the plaque encompassed the IVUS imaging catheter, the lumen diameter and CSA were assumed to be the size of the catheter. The reference segments selected were the most normal appearing cross sections within 10 mm proximal and distal of the stented segment.

Statistical analysis. Statistical analysis was performed using SPSS for Windows 7.5 (SPSS, Chicago, Illinois) and SAS (Statistical Analysis System, Cary, North Carolina). Continuous data are presented as mean ± SD. Comparisons between groups were performed by use of paired or unpaired *t* tests or analysis of variance for repeated measures with post hoc analysis for continuous variables. Qualitative data are presented as frequencies and comparison between quantitative data was performed with chi-square statistics. Initially, simple linear regression analysis was performed to evaluate the relationship between the minimal lumen diameter obtained by IVUS and QCA. Furthermore, the limits of agreement between pairs of measurements were determined according to the method described by Bland and Altman (15). The mean difference between the methods investigated is the systematic error (bias) and two standard deviations are defined as limits of agreement (95% confidence interval). Predictors of restenosis were calculated by univariate and multivariate logistic regression analysis. A p value <0.05 was considered statistically significant.

RESULTS

Procedural results. Procedural success was achieved in all patients. All QCA measurements are listed in Table 1. There were no significant creatine kinase elevations or major in-hospital complications (death, bypass surgery, additional angioplasty or Q-wave myocardial infarction). Patients were discharged 2.5 ± 1.0 days after the procedure.

Mechanisms of rotablation and adjunct angioplasty. Planar intravascular ultrasound measurements (Table 1) revealed a significant increase in minimal lumen CSA by rotablation. This acute lumen gain was a result of a decrease in IH CSA. The stent CSA, the peristent plaque CSA and the EEM CSA did not change significantly from baseline to

after RA. The MLD after RA as assessed by IVUS (1.75 ± 0.34 mm) remained 15 ± 4% smaller than the burr diameter used (final burr size: 2.05 ± 0.5 mm), indicating acute plaque recoil. The mean lumen diameter (2.25 ± 0.22 mm) was 10 ± 5% larger than the final burr size used.

After adjunct angioplasty the minimal lumen CSA increased significantly as a result of an increase in stent CSA and a decrease in IH CSA. Conversely, the maximal area of stenosis decreased from 54 ± 21% to 38 ± 12%. Both the peristent plaque CSA and the EEM CSA increased also from after RA to after angioplasty.

The contribution of plaque removal, stent expansion and plaque extrusion to the overall periprocedural lumen gain was as follows: 1) plaque removal (during RA), 37 ± 11%; 2) further stent expansion, 49 ± 15%; 3) plaque extrusion 14 ± 10 (during adjunct angioplasty).

Angiographic six-month follow-up and predictors for recurrent restenosis. Angiographic follow-up was available in 40/45 (89%) patients. Recurrent restenosis was observed in 18/40 patients (45%). Clinical follow-up after 6.6 ± 2.5 months was available for all patients and revealed a rate of recurrent revascularization of 38% (17/45). Four variables were identified as predictors of recurrent restenosis at six-month angiographic follow-up: percent diameter stenosis before intervention (83 ± 22% vs. 72 ± 17%, $p < 0.01$), stent length (40.5 ± 21.3 mm vs. 21.5 ± 14.1 mm, $p < 0.001$), total lesion length (35.1 ± 20.2 mm vs. 15.2 ± 14.1 mm, $p < 0.001$) and the amount of neointimal recoil after RA (23.2 ± 13.6% vs. 8.9 ± 8.3%, $p < 0.001$). The only independent predictor by multivariate analysis, however, was neointimal recoil ($p < 0.01$, $r^2 = 0.44$). Other clinical (age, gender, diabetes, lesion location, stent type), procedural (burr/artery ratio), angiographic (vessel size, diameter stenosis) or IVUS variables (amount of plaque ablation, intimal hyperplasia) were statistically not associated with recurrent angiographic restenosis.

Comparison of MLD measurements obtained by IVUS and QCA analysis. All lesions with an angiographic MLD less than the IVUS catheter (<1 mm) had to be excluded; therefore, a subset of 18 lesions were included with regard to preinterventional diameters. For comparative measurements after RA and after adjunct angioplasty, the minimal lumen diameters of all 49 lesions were available for analysis (Fig. 1). Simple linear regression analysis showed low correlation coefficients between the two methods throughout the whole procedure (r value: 0.39 to 0.57). The IVUS values before intervention and after RA were systematically higher than the corresponding angiographic values (Fig. 1 A and B). In contrast, there was no systematic bias between QCA and IVUS after adjunct angioplasty despite a low correlation coefficient ($r = 0.39$, Fig. 1 C).

DISCUSSION

The results of this study indicate that:

1. Rotablation effectively ablates in-stent plaque (IH) without further stent expansion, stent destruction or external vessel stretch.
2. The MLD after rotablation remains smaller than expected from the burr size used, indicating acute plaque recoil.
3. Adjunct angioplasty after RA leads to additional lumen gain by further stent expansion and, to a lesser extent, plaque extrusion.
4. The rate of recurrent restenosis at six-month angiographic follow-up is 45%, with a target vessel revascularization rate of 40%. Lesion and stent length, smaller lesion diameters and amount of acute neointimal recoil after RA are predictors of recurrent restenosis at six-month angiographic follow-up.
5. There is a low correlation between QCA and IVUS analysis, especially for postinterventional measurements and a systematic underestimation of the MLD by QCA before intervention and after RA.

Mechanisms of "tissue-debulking" by rotablation for in-stent restenosis. In the present study, planar IVUS measurements revealed that RA effectively ablates in-stent neointimal tissue and contributes 37 ± 11% to the overall procedural lumen gain when adjunct angioplasty is performed. An example of the complex clinical situation is shown in Figure 2. Neointima tissue usually is inhomogeneously distributed and the rotablator only removes those portions of the plaque that are occlusive enough to be accessible for the device (focal plaque ablation). Large sections of the stent will not be effectively treated by the burr, although there is significant plaque burden.

The MLD after RA assessed by IVUS was 15 ± 4% smaller than the burr diameter used, indicating acute neointimal recoil; however, the mean lumen diameter after RA was 10 ± 5% larger. Most of this recoil occurred in our experience in those stent segments with severe tissue burden or even total occlusion before intervention. Additionally, ineffective cutting sometimes results from fast "skipping" of the burr into distal stent segments during the procedure. Plaque recoil may be a significant phenomenon as it obviously occurs in those segments of the lesion that have already shown the strongest tendency for restenosis. In addition, acute recoil quantitatively reduces the potential ablating effect and the primary possible procedural success of the rotablator and was also shown to be a risk factor for recurrent restenosis in this study.

Similar phenomena have also been described for nonstented, noncalcified lesions treated by RA (11,16). This is in contrast to fibrotic and calcified lesions, in which effective plaque removal without elastic recoil has been demonstrated by IVUS (10). The differences between noncalcified and calcified coronary lesions in their response to high speed rotational atherectomy may be explained in part by the principle of "differential cutting" by which the rotablator is thought to act.

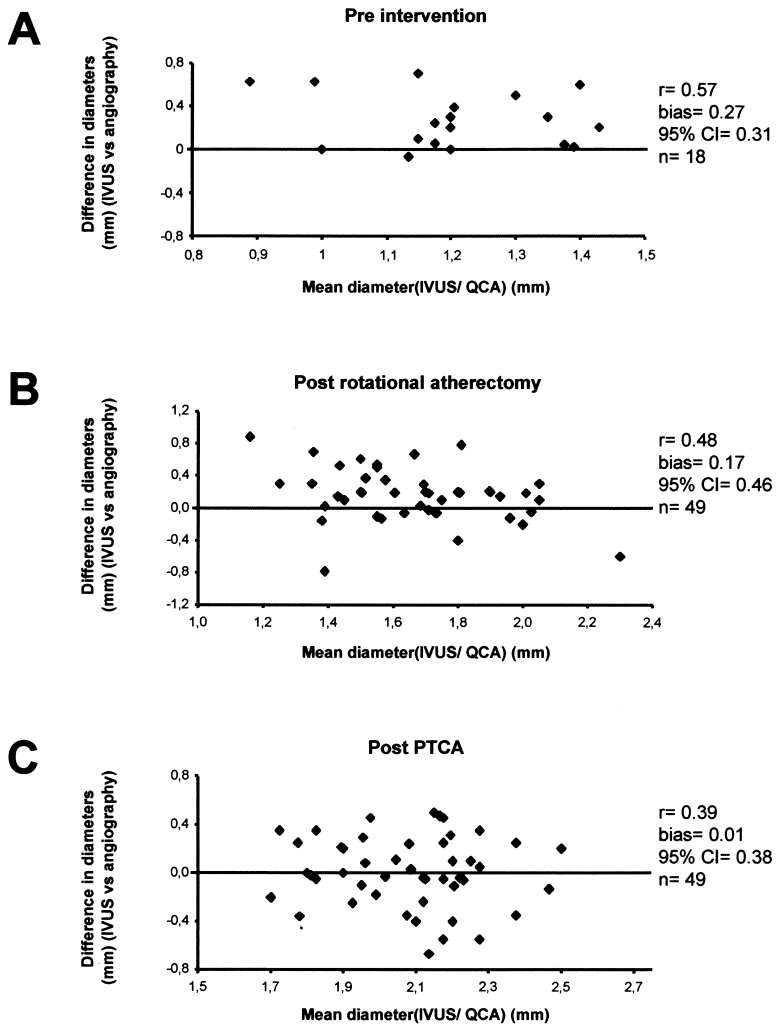

Figure 1. Comparison of minimal lumen diameter measurements obtained by intravascular ultrasound (IVUS) and quantitative coronary angiography (QCA) before intervention **(A),** after rotational atherectomy **(B)** and after percutaneous transluminal coronary angioplasty (PTCA) **(C)** using the Bland-Altman method. The individual differences between pairs of measurements (on the y-axis) are plotted against the mean value of IVUS and QCA (on the x-axis). CI = confidence interval.

Adjunct angioplasty after RA. Adjunct angioplasty after RA contributes 63 ± 16% to the overall procedural lumen gain mainly by further stent expansion (77 ± 14%) and, to a smaller degree, by tissue extrusion through the stent struts (23 ± 11%). The residual mean and maximal area stenosis after adjunct low pressure angioplasty are 30 ± 19% and 38 ± 12% respectively. The relatively high residual area stenosis may be caused by the inflation pressure (7 ± 1 atm) used in this series of patients. This relatively low inflation pressure was intended to reduce additional vessel trauma with potentially beneficial long-term effects (recurrent restenosis rates). Adjunct high pressure angioplasty (>15 atm) might result in favorable acute angiographic results; however, the postprocedural lesion diameter was not a predictor of recurrent restenosis at six-month angiographic follow-up.

Comparison with DCA and ELCA as alternative debulking techniques. Directional coronary atherectomy (DCA) provides the only technique that may be able to completely remove in-stent neointima; however, aggressive debulking utilizing this device may be associated with stent destruction (17,18). In contrast, RA did not result in stent destruction or migration. Excimer laser coronary angioplasty (ELCA) for in-stent restenosis results in a lower overall target vessel revascularization rate compared with angioplasty alone, supporting the concept of tissue debulking (19). The mechanisms of ELCA for the treatment of in-stent restenosis have recently been described in detail with 29 ± 15% of the procedural lumen gain contributable to atheroablation (19), compared with 37 ± 11% when RA is used for debulking as demonstrated in this study. Preliminary comparative data also indicated that RA leads to a greater decrease in IH volume than ELCA (20).

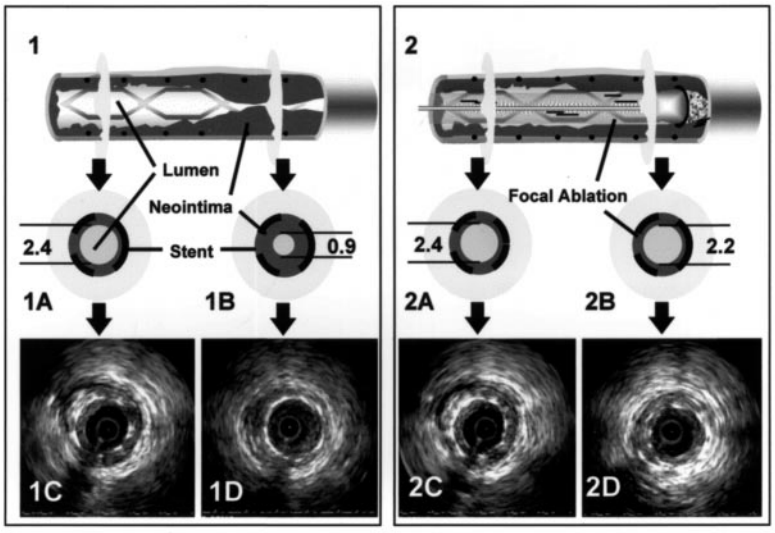

Figure 2. Relation between in-stent neointima distribution and focal plaque ablation. Due to inhomogeneous plaque distribution and focal neointima accumulation **(1A, 1B)** the minimal lumen diameter before rotablation ranges between 0.9 mm **(1D)** and 2.4 mm **(1C)** by intravascular ultrasound. Rotational atherectomy (burr size 2.38 mm) does not induce further plaque ablation in those parts of the stent with a larger lumen **(2A, 2C),** even though there is significant plaque burden. Focal plaque ablation **(2B)** leads to an increase in the minimal lumen diameter and cross-sectional area as shown by intravascular ultrasound **(2D)**; however, the final burr/lumen ratio >1 indicates acute neointimal recoil.

Treatment of in-stent restenosis by angioplasty alone. When angioplasty is used as a stand-alone procedure in the treatment of in-stent restenosis, further stent expansion quantitatively accounts for more than half of the total lumen enlargement as compared with the decrease in neointimal tissue burden (56 ± 28% vs. 44 ± 28%) (21). The amount of tissue extrusion or compression induced by adjunct angioplasty was smaller in the present series as RA induced significant tissue ablation and therefore reduced the volume of in-stent tissue available for extrusion/compression. In addition, the maximal pressure used for adjunct angioplasty in this study was lower (7 ± 1 atm) than for angioplasty alone (>10 atm) and the balloon size for adjunct angioplasty after RA was the same as for primary stent implantation.

The restenosis rate after angioplasty of focal lesions is reported to be as low as 22% (6). In lesions of intermediate length (length: 8.93 ± 7.30 mm), target vessel revascularization rates are significantly higher (38%) (19). Rotational atherectomy with adjunct angioplasty results in an improved long-term clinical outcome compared with angioplasty alone in the setting of diffuse ISR (clinical recurrence 25% vs. 47% at six months) as reported in the first comparative study (22). Additionally, in diffuse lesions treated by angioplasty alone, recurrent restenosis rates may be as high as 80% (8). In light of the latter results, a restenosis rate of 45% in long lesions (22.4 ± 20.2 mm) appears to be favorable; however, additional antiproliferative pharmacotherapy or intravascular brachytherapy may further improve long-term outcome after treatment of ISR.

Predictors of recurrent restenosis. Based on the quantitative analysis of the angiographic follow-up, stent and lesion length and preinterventional diameter stenosis were identified as predictors of recurrent restenosis after six months. The predictive value of serial stent implantation, and thereby lesion length, on restenosis rates has been described for primary stent implantation (23) and turns out to be a risk factor in the clinical setting of RA for in-stent restenosis as well.

Most interestingly, the amount of acute neointimal plaque recoil was also identified as a predictor of restenosis after rotablation. Recoil after RA as an instantaneous "restenosis" mechanism obviously reflects an unfavorable lesion response to the rotablator for unknown reasons.

However, a high burr/artery ratio or the absolute amount of tissue debulking, as suggested by Sharma et al. (24), could not be proven to have beneficial effects on restenosis rates in our small series of patients.

Study limitations.

1. Stents treated in this study comprised four types of stents with different physical properties with regard to the radial and longitudinal forces possibly influencing the effects of adjunct angioplasty. The type of stent, however, was not a predictor of recurrent restenosis.
2. This study reflects an operator learning curve with a tendency to use smaller burr sizes and guiding catheters in the first series of patients. Therefore, the amount of RA-induced tissue ablation and the contribution of RA to the overall procedural lumen gain may be higher in

patients currently treated by RA with adjunct angioplasty.
3. The number of patients included in this study is still relatively small; larger trials are needed to confirm the present results and probably to identify further predictors of recurrent restenosis.
4. The clinical and angiographic end point of this study was at six months. The long-term outcome after RA of in-stent restenosis is yet unknown.
5. There is no control group as all data were obtained in a consecutive series of patients usually with long and diffuse in-stent restenosis, in whom angioplasty as a stand-alone procedure was not considered appropriate.

Conclusions. Rotational atherectomy of in-stent restenosis leads to significant atheroma ablation of neointima supporting the concept of "tissue-debulking." Angiographic restenosis is observed in 45% of patients with diffuse lesions. Stent and lesion length, preinterventional diameter stenosis and acute neointimal recoil are predictors of angiographic restenosis. Differences between angioplasty as a stand-alone procedure compared with RA with adjunct angioplasty and other debulking techniques in the treatment of diffuse in-stent restenosis are yet unknown. Several randomized trials have been initiated to provide insight into the acute and long-term effects of the different treatment modalities.

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